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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,131	KELER ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-39 is/are rejected.

7)☒ Claim(s) 35 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment filed on 2/10/05 canceled claims 1-26 and 40-45. Claims 27-39 are currently pending and under examination in the instant application. An action on the merits follows.

Priority

The applicant has submitted an application data sheet (ADS) which indicates that this application is a continuation of U.S. Application 09/203,958. However, applicant has not amended the first paragraph of the specification, which recites the claim for benefit of priority, to include a reference to this parent application. The specification on page 1 only refers to provisional application 60/067,232. Applicant is required update the specification to add a reference to the 09/203,958 parent, including the relationship between the parent and the instant application and the status of the parent application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-34 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of increasing an immune response comprising the use of a cell transformed to express on its cell surface a "component" which binds to an Fc receptor or which has been transformed to comprise a nucleic acid encoding a protein which binds to an Fc receptor. The specification does not provide sufficient written description for the genus of components or proteins which bind to an Fc receptor as claimed. The specification discloses that components capable of binding an Fc receptor include anti-Fc receptor antibodies, peptide mimics of an antibody, chemical compounds, or engineered binding proteins. However, the specification does not provide sufficient description for any component or protein capable of binding to an Fc receptor other than an anti-Fc receptor antibody. The specification does not provide any particular description in terms of structural, chemical, or physical properties of any chemical or protein other than an Fc receptor antibody. In regards to chemical compounds, the specification discloses the use of a cyanidin reagent. However, the claims under examination are limited to transformed cells, which the specification on page 7 defines as cells into which a nucleic acid or expression vector have been introduced. A cyanidin reagent cannot be encoded by a nucleic acid. Therefore, the specification provides no description of any chemical that can be encoded by a nucleic acid and which binds to an Fc receptor other than a polypeptide.

The specification further does not disclose any particular peptide mimic, or engineered binding protein or provide sufficient description as to the particular structural properties of an Fc receptor binding peptide mimic or engineered binding protein such that the skilled artisan would be able to recognize proteins or peptide mimics which are capable of binding an Fc receptor. While it is noted that the specification on page 6 states that an Fc receptor engineered binding protein could be obtained from a variegated protein display library, the specification does not provide any actual description of any engineered binding protein present in any of variegated protein display library. Thus, of the vast numbers of potential nucleic acid sequences encoding an Fc receptor binding component or protein which are encompassed by the claims, the specification only provides adequate written description for anti-Fc receptor antibodies. The specification fails to provide any specific description of any peptide mimic or engineered binding protein or a nucleic acid encoding a peptide mimic or engineered binding protein including sequence or structural information, and further fails to provide an guidance as to active domains or structures in peptide mimics or engineered binding proteins which are responsible for their biological activity such that nucleic acid sequences encoding these proteins could be identified or isolated. In the absence of such description, the skilled artisan cannot envision the detailed chemical structure of the sequences which comprise any protein capable of binding an Fc receptor other than an anti-Fc receptor antibody.

The Revised Interim Guidelines state, " when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus .....In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2,

page 71436, or the Revised Interim Guidelines for Written Description). Further, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The applicant has not provided any description or reduction to practice of components capable of binding to an Fc receptor other than an anti-Fc receptor antibody. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of nucleotide

sequences which encode Fc receptor binding proteins as defined by the specification. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Thus, for the reasons outlined above, the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph.

Claims 33 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising the transformation of cells expressing a particular antigen *in vitro*, does not reasonably provide enablement for methods of transforming specific cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of increasing an immune response to an antigen comprising the step of transforming a cell which expresses the antigen with a nucleic acid encoding a protein which binds to an Fc receptor on an effector cell. The specification discloses that the cells expressing the antigen can be transformed either *in vitro* or *in vivo*. As a preferred embodiment of the invention, the specification discloses that tumor cells expressing a tumor antigen can be transformed with an expression vector encoding a single chain Fv derived from either the H22 or A77 antibodies which recognize FcR linked to the transmembrane domain of the PDGF receptor.

The specification does not provide an enabling disclosure for the targeted transformation of particular cell types *in vivo*. As noted above, the specification discloses that tumor cells or

cells expressing a particular tumor antigen can be transformed *in vivo*. The specification does not provide sufficient guidance for targeted *in vivo* gene delivery. At the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target the disclosed expression constructs to any particular cell type or to tumors or cells expressing tumor antigens in particular. Therefore, in view of the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing, the absence of guidance provided by the specification, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to transform specific cells *in vivo*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 35 recites the method of claim 35, and thus depends upon itself. Thus, no actual method steps are recited. As such the metes and bounds of the claim cannot be determined. It is suggested that the claim dependency be amended to recite the appropriate parent claim.

Claims 35 is further objected to because of the following informalities: Claim 35 depends upon itself, and thus is an improper dependent claim. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27 and 31-35, and 38-39 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/20048 (June, 5, 1997), hereafter referred to as Ledbetter et al. The applicant claims methods of increasing an immune response in a subject comprising administering to the subject a

tumor cell transformed ex vivo to express on its surface a component which binds to an Fc receptor of an effector cell, and methods of increasing an immune response to an antigen by transforming a cell expressing a tumor antigen ex vivo with a nucleic acid encoding an antibody which binds to an Fc receptor and contacting the cell with an effector cell in the presence of a lymphocyte in vivo.

Ledbetter et al. teaches the construction of recombinant expression vectors which comprise a fusion protein comprising an a single chain Fv molecule operatively linked to a transmembrane domain of a cell surface receptor and the use of said vector to transfect cells *in vitro/ex vivo* (Ledbetter et al., pages 6-7, page 12, lines 14-20, and page 21). Ledbetter et al. further teaches that the single chain Fv binds FcγR , FcαR, or FcεR, including CD64 which is FcγRI (Ledbetter et al., pages 6-7, bridging paragraph). Ledbetter et al. further teaches that the transfected cells expressing the single chain Fv fusion protein on the cell surface can be used in *ex vivo* or *in vivo* methods for enhancing a T cell response in a subject (Ledbetter et al., page 12). In particular, Ledbetter et al. teaches that autologous or allogeneic cells, such as tumor cells, are genetically modified to produce the sFV on the cell surface *ex vivo* and then administered to the subject to stimulate a T cell response (Ledbetter et al., page 12, lines 20-30). Please note that as mammalian subjects have effector cells and lymphocytes, administering tumor cells genetically modified to produce the sFV on the cell surface to a subject constitutes "contacting the cell with an effector cell in the presence of a lymphocyte". Note as well that a tumor cell naturally comprises tumor antigens. Thus, by teaching all the limitations of the claims as written, Ledbetter et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/20048 (June, 5, 1997), hereafter referred to as Ledbetter et al., in view of WO 91/00360 (January 10, 1991), hereafter referred to as Fanger et al.. The applicant claims methods of increasing an immune response in a subject comprising administering to the subject a tumor cell transformed *ex vivo* to express on its surface a component which binds to an Fc receptor of an effector cell and an agent which increases expression of Fc receptors on effector cells.

Ledbetter et al. teaches the construction of recombinant expression vectors which comprise a fusion protein comprising an a single chain Fv molecule operatively linked to a transmembrane domain of a cell surface receptor and the use of said vector to transfect cells *in vitro/ex vivo* (Ledbetter et al., pages 6-7, page 12, lines 14-20, and page 21). Ledbetter et al. further teaches that the single chain Fv binds FcγR , FcαR, or FcεR, including CD64 which is FcγRI (Ledbetter et al., pages 6-7, bridging paragraph). Ledbetter et al. further teaches that the transfected cells expressing the single chain Fv fusion protein on the cell surface can be used in *ex vivo* or *in vivo* methods for enhancing a T cell response in a subject (Ledbetter et al., page 12). In particular, Ledbetter et al. teaches that autologous or allogeneic cells, such as tumor cells, are genetically modified to produce the sFV on the cell surface *ex vivo* and then administered to the subject to stimulate a T cell response (Ledbetter et al., page 12, lines 20-30). Please note that as

mammalian subjects have effector cells and lymphocytes, administering tumor cells genetically modified to produce the sFV on the cell surface to a subject constitutes "contacting the cell with an effector cell in the presence of a lymphocyte". Note as well that a tumor cell naturally comprises tumor antigens.

Ledbetter et al. differs from the instant invention by not teaching the administration of an agent to increase the expression of Fc receptors on effector cells. Fanger et al. supplements Ledbetter et al. by teaching that in related method of inducing immune responses by targeting effectors cells with an antibody the binds to the Fc receptor, it is useful to pretreat the effectors cells, such as macrophages, with IFN-gamma and/or TNF, IL-2 and colony stimulating factor (Fanger et al., page 10). Fanger et al. provides motivation for treating the effector cells with IFN-gamma or other cytokines by teaching that IFN-gamma increases the number of Fc receptors for attachment to the targeting antibody and that cytokines such as TNF further activate the effector cell (Fanger et al., page 10). Thus, in view of the motivation to increase targets for antibodies specific for Fc receptors by treating cells with IFN-gamma provided by Fanger et al., it would have been *prima facie* obvious to the skilled artisan to further administer IFN-gamma to a subject to increase Fc receptor expression on effector cells and thus increase the number of targets for the tumor cells expressing the sFV antibodies on the cell surface in the methods of Ledbetter et al. with a reasonable expectation of success.

Claims 33 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/20048 (June, 5, 1997), hereafter referred to as Ledbetter et al. in view of Guyre et al. (1997) Canc. Immunol. Immunther., Vol. 45, 146-148. The applicant claims methods of increasing an

immune response to an antigen by transforming a cell expressing a tumor antigen ex vivo with a nucleic acid encoding an antibody which binds to an Fc receptor and contacting the cell with an effector cell in the presence of a lymphocyte in vivo, wherein the antibody is a single chain Fv fragment, specifically a single chain Fv derived from the humanized antibody H22.

Ledbetter et al. teaches the construction of recombinant expression vectors which comprise a fusion protein comprising an a single chain Fv molecule operatively linked to a transmembrane domain of a cell surface receptor and the use of said vector to transfect cells *in vitro/ex vivo* (Ledbetter et al., pages 6-7, page 12, lines 14-20, and page 21). Ledbetter et al. further teaches that the single chain Fv binds FcγR , FcαR, or FcεR, including CD64 which is FcγRI (Ledbetter et al., pages 6-7, bridging paragraph). Ledbetter et al. further teaches that the transfected cells expressing the single chain Fv fusion protein on the cell surface can be used in *ex vivo* or *in vivo* methods for enhancing a T cell response in a subject (Ledbetter et al., page 12). In particular, Ledbetter et al. teaches that autologous or allogeneic cells, such as tumor cells, are genetically modified to produce the sFV on the cell surface *ex vivo* and then administered to the subject to stimulate a T cell response (Ledbetter et al., page 12, lines 20-30). Please note that as mammalian subjects have effector cells and lymphocytes, administering tumor cells genetically modified to produce the sFV on the cell surface to a subject constitutes "contacting the cell with an effector cell in the presence of a lymphocyte". Note as well that a tumor cell naturally comprises tumor antigens.

Ledbetter et al. does not specifically teach the H22 antibody which recognizes CD64. Guyre et al. supplements Ledbetter et al. by teaching the H22 antibody and its use in generating fusion proteins with gp120 or tetanus toxin (Guyre et al., page 148, column1, paragraphs 2-3),

Guyre et al. provides motivation for using the H22 antibody in the single chain fusion protein taught by Ledbetter et al. by teaching that the H22 antibody binds to CD64 outside the ligand - binding domain of the receptor such that the binding of H22 is not inhibited by serum IgG (Guyre et al., page 148, column 1, paragraph 3). Thus, based on the motivation to use the H22 antibody in order to bind CD64 outside of the Fc binding domain as taught by Guyre et al., it would have been *prima facie* obvious to the skilled artisan to use the H22 antibody as the Fc binding portion of the chimeric molecules taught by Ledbetter et al. Further, in view of the high level of skill in molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success of making and using cells expressing a chimeric molecule comprising H22 according to the teachings of Ledbetter et al. in view of Guyre et al.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for

electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER